REMARKS

Claims 10 and 15 are cancelled herein without prejudice or disclaimer and Applicant reserves the right to claim subject matter of the cancelled claims in one or more continuing patent applications. Claims 1, 3-9, 11 and 12 are amended herein and claims 49-53 are new. Basis for the amendments and the newly claimed subject matter is in the claims as originally filed and in specification throughout. Representative basis for polymorphic positions is in paragraphs 00215 and 00223 of the specification, for example. Representative basis for identifying intronic polymorphic positions is in Figures 1A-1AAA and in paragraph 0090 (and paragraphs 0011, 0034 and 00214) of the specification, for example. Accordingly, entry of the claim amendments and new claims will not introduce any prohibited new matter.

The Office rejected claims in the outstanding action for alleged anticipation, alleged lack of written description and alleged lack of enablement, which are summarized hereafter:

i. Claims 1, 2, 13 and 15 were rejected under 35 U.S.C. 102(e) for alleged anticipation over Stratton (US2004/0096855);
ii. Claims 1-4, 10, 13 and 15 were rejected under 35 U.S.C. 102(f) due to an alleged inconsistency set forth in Myer (*J. Carcinogenesis 2*: 1-5 (2003));
iii. Claims 1-4, 10 and 13-15 were rejected under 35 U.S.C. 112, first paragraph, for the specification allegedly lacking a written description; and
iv. Claims 1-4, 10 and 13-15 were rejected under 35 U.S.C. 112, first paragraph, for the specification allegedly lacking an enabling disclosure.

Claim rejections in the outstanding Office action are traversed and are moot in view of the amendments herein. Applicant does not necessarily accept or agree with rejections set forth in the Office action, and the claim amendments, claim cancellations and new claims are submitted herein for the purpose of expediting prosecution. Remarks in response to the outstanding claim rejections and objections are set forth hereafter.

Election and Restriction Requirement

Amended claim 1 specifies one or more polymorphic variants are detected in an intron within a particular region of a human nucleic acid sample. Amended claim 3 lists polymorphic variants associated with melanoma in Table 7 and Table 9. The polymorphic variants listed in amended claim 3 are located in introns of the region specified in amended claim 1. Subject matter of amended claim 1 therefore is a linking claim and is generic to the polymorphic variants listed in amended claim 3 and other dependent claims. Applicant notes the elected polymorphic position, position 146311 in SEQ ID NO: 1 corresponds to the position of the polymorphic site designated by rs1639679.

Information Disclosure Statement

Applicant will address the Office's comments regarding the information disclosure statement under separate cover.

Objections to the Specification

The Office objected to the specification for containing embedded hyperlinks. Text containing the term "www" has been replaced in the specification with "World Wide Web" to remove terms that might be interpreted as embedded hyperlinks.

Claim Objections

The Office objected to claim 3 for grammatical informalities. Claim 3 is amended herein and no longer includes the phrase objected to in the Office action.

Rejection for Alleged Anticipation Over Stratton

Claims 1, 2, 13 and 15 were rejected under 35 U.S.C. 102(e) for alleged anticipation over Stratton (US2004/0096855). This rejection is inapplicable to the claims as amended because Stratton fails to address a polymorphic variant in an intron of *BRAF*. Stratton also does not address any of the particular intronic polymorphic positions

claimed herein. Applicant therefore respectfully requests withdrawal of the rejection under 35 U.S.C. 102(e).

Rejection for Alleged Anticipation Over Myer

Claims 1-4, 10, 13 and 15 were rejected under 35 U.S.C. 102(f) due to an alleged inconsistency set forth in Myer (*J. Carcinogenesis 2*: 1-5 (2003)). Applicant does not believe there is an inconsistency between the inventorship designated in the subject patent application and the authorship of the Myer publication as the latter states in the "Acknowledgements" section on page 4:

> We acknowledge the contribution to the study design (genome-wide SNP scan) and execution of the experiment by Sequenom, Inc., San Diego, CA, USA.

The named inventors developed the claimed subject matter for Sequenom, Inc., the assignee of the present patent application. The undersigned understands at this time that the named inventors:

1. identified the claimed method for development;
2. selected the polymorphic positions screened;
3. requested nucleic acid samples from Mr. Myer;
4. selected a subset of nucleic acid samples for screening from the set of samples provided by Mr. Myer;
5. screened the subset of samples using the selected polymorphisms;
6. analyzed the screening data; and
7. determined which of the polymorphic variants and haplotypes were associated with melanoma.

Thus, the undersigned understands that Mr. Myer's involvement was limited to providing nucleic acid samples at the request of the named inventors. The undersigned also understands that Mr. Myer had access to data generated by the named inventors. The undersigned further understands the remaining authors of the Myer document had no involvement with development of the claimed methods, other than possibly having an

involvement with the nucleic acid samples forwarded to the named inventors. Applicant therefore respectfully requests withdrawal of the rejection under 35 U.S.C. 102(f).

Rejection for Alleged Lack of Written Description

The Office rejected claims 1-4, 10 and 13-15 for the specification allegedly lacking a written description of the claimed subject matter. Applicant respectfully notes the rejection is inapplicable to claims 10 and 15 as they are cancelled herein without prejudice or disclaimer. The rejection is inapplicable to the remaining claims as amended and the rejection is traversed in view of the reasoning presented hereafter.

Well-accepted principles of genetics support a finding that Applicant's specification provided a written description of the claimed subject matter at the time of filing. The concept of linkage disequilibrium in genetics embodies the phenomenon that a disease-associated region in the human genome contains a cluster of polymorphisms associated with a disease state. Specifically,

> markers very close to the disease gene will tend, more likely than average, to retain the haplotype of the original chromosome because, as the distance to the disease gene shrinks, it becomes less likely that recombination events will have occurred in this particular region.

From Cantor & Smith, *Genomics: The Science and Technology Behind the Human Genome Project*, 1999, John Wiley & Sons, Inc., New York, page 192. Thus, identifying multiple polymorphisms associated with a disease state within a region also identifies the region as associated with the disease state consistent with the concept of linkage disequilibrium.

The specification analyzed several intronic polymorphisms in the region of the human genome specified by claim 1 – the position of rs1267618 to the position of rs1639679 – and identified several associated with melanoma. For example, please see Tables 7 and 9 on pages 65 to 67 of the specification, which identify ten (10) intronic polymorphisms associated with melanoma with a p-value of less than 0.05 of the twelve

(12) intronic polymorphisms analyzed in the claimed region. Thus, the specification provided a written description for the claimed subject matter because Applicant identified a region associated with melanoma by virtue of identifying several polymorphisms associated with melanoma in that region.

Applicant therefore respectfully asserts it analyzed a representative number of polymorphic positions in the claimed region. Applicant further identified a representative number of polymorphic variants associated with melanoma in the region.

Further, Applicant analyzed haplotypes within the claimed region and determined polymorphic variants associated with melanoma at positions 68398, 76779, 138875 and 146311 in SEQ ID NO: 1 were in strong linkage disequilibrium (LD). These positions correspond to rs1267621, rs1267606, rs1267646 and rs1639679, respectively, and data is presented in paragraphs 00225 to 00228. These four polymorphic variants are located at the termini of the claimed region and the finding of strong LD provides evidence that the claimed region is significantly associated with melanoma. Also, the population sizes for the haplotype study are significant as there was a combined melanoma population of 1000 individuals and a combined control population of 898 individuals (e.g., Table 13).

Accordingly, the specification provides significant evidence that the claimed region was associated with melanoma and that Applicant had possession of the claimed subject matter. Therefore, withdrawal of the rejection under 35 U.S.C. 112, first paragraph, for alleged lack of written description respectfully is requested.

Rejection for Alleged Lack of Enablement

The Office rejected claims 1-4, 10 and 13-15 for the specification allegedly lacking an enabling disclosure of the claimed subject matter. Applicant respectfully notes the rejection is inapplicable to claims Applicant respectfully notes the rejection is inapplicable to claims 10 and 15 as they are cancelled herein without prejudice or disclaimer. The rejection is inapplicable to the remaining claims as amended and the rejection is traversed in view of the reasoning presented hereafter.

Applicant's specification identifies a region specified in claim 1 associated with occurrence of melanoma. Given the discussion regarding genetics principles above,

Applicant's finding paves the way towards identifying and using polymorphisms of this region in the claimed methods. Applicant's finding that the intronic polymorphisms in the region specified in claim 1 are associated with melanoma guides the person of ordinary skill in the art towards routinely identifying any other intronic polymorphisms associated with melanoma in that region. The routine nature of any experimentation extending beyond the results described in Applicant's specification is underscored by the clear teachings and guidance in the specification, as elucidated hereafter.

The specification provides multiple working examples in support of the claimed subject matter, an *Ex Parte Foreman* factor bearing on enablement addressed in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). For example,

(i) paragraphs 00212 to 00224 describe methods and components for identifying intronic polymorphisms associated with melanoma in DNA from a subject in the region specified by claim 1;

(ii) paragraphs 00225-00233 describe methods for identifying haplotypes of intronic polymorphisms associated with melanoma;

(iii) paragraphs 00208 to 00209 describe methods for isolating DNA from human blood samples.

In addition to this set of working examples for performing the claimed methods, the specification also provides clear guidance to the person of ordinary skill in the art for the scope of the claimed subject matter, another factor addressed in *In re Wands* (supra). For example, the specification in paragraphs 0094 to 0098 provides clear guidance for performing multiple types of methods useful for identifying polymorphisms associated with melanoma.

The Court of Appeals for the Federal Circuit (CAFC) has found some experimentation is acceptable to produce an invention, and routine experimentation does not preclude a finding of enablement (*e.g.*, *Monsanto Co. v. Scruggs*, 459 F.3d 1328; 79 USPQ.2d 1813 (Fed. Cir. 2006) and *In re Wands* (supra)). Given that the working examples and clear guidance in the specification teach multiple methods for identifying intronic polymorphisms associated with melanoma, the person of ordinary skill in the art

could apply these methods in a routine manner to intronic polymorphisms in the region specified by claims 1 and perform the claimed methods.

The facts and reasoning on which the CAFC found enablement in *In re Wands* are applicable to the same finding of enablement here. In the *Wands* case, the Office erred in rejecting the Applicant's claim to immunoassay methods using a specified generic class of antibodies. The Applicant made a public deposit of a hybridoma cell line that secreted only a specific antibody, yet the CAFC found those skilled in the monoclonal antibody art could, using the state of the art and Applicant's written disclosure, produce and screen other hybridomas secreting other monoclonal antibodies falling within the generic class without undue experimentation.

The technology in *Wands* is similar to the technology described in the present specification in that the person of ordinary skill in the art is prepared to screen additional intronic polymorphisms in the region specified by claim 1. The specification has disclosed a region of the human genome associated with melanoma, and the person of ordinary skill in the art now (i) is guided to that region, and (ii) is motivated to routinely identify any other polymorphisms in the region associated with melanoma, should they exist. Further, multiple screening methods are well-known in the art, as described above, and suited to automated screening platforms. Thus, the rationale in *In re Wands* is applicable to a finding of enablement here.

These factors, coupled with the high level of skill in the art for technology pertaining to the pending claims, leads to the conclusion that any experimentation associated with the full claim scope is routine and not undue. Accordingly, the specification provides an enabling disclosure of the claimed subject matter consistent with 35 U.S.C. 112, first paragraph. Applicant therefore respectfully requests withdrawal of the rejection.

CONCLUSIONS

Applicant respectfully submits all pending claims will be in condition for allowance upon entry of the amendments herein. Applicant respectfully solicits a prompt notification to this effect, and the Examiner is encouraged to contact the undersigned representative (contact information below) to promptly resolve any remaining issues or questions.

In the unlikely event a relevant document is separated from this Amendment and the Office determines that an extension and/or other relief is required, Applicant petitions for any required relief, including extensions of time, and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-3473**.

Respectfully submitted,

Dated: May 28, 2007

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